Discrepancy between guidelines for stroke prevention in atrial fibrillation and practice patterns in primary care. The nationwide French AFIGP survey

Différences observées entre les recommandations chez les patients présentant une fibrillation atriale et les stratégies thérapeutiques en médecine générale. Données du registre français AFIGP

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Atrial fibrillation; General practitioners; Guidelines; Antithrombotics

Summary
Background. — General practitioners (GPs) play a pivotal role in the long-term management of patients with atrial fibrillation (AF), including anticoagulant prophylaxis for stroke prevention.
Aims. — To investigate the antithrombotic prescription behaviours of GPs in France and compare them with the European Society of Cardiology (ESC) guidelines for stroke prevention, and to identify the major determinants of use of antithrombotic therapy.
Methods. — We conducted a cross-sectional survey, using data from the French Longitudinal Patient Database, on the use of antithrombotic treatments for stroke prevention in 15,623 patients (≥18 years of age) with AF who attended at least one GP consultation between July 2010 and June 2011. Data were collected on patient baseline characteristics, stroke risk factors, and prescription of antithrombotic drugs.
Results. — The mean age was 74.6 ± 11.1 years, 59.5% were men, and 83.1% had a CHADS2 score ≥ 1. Over half (52.6%) of the patients with a CHADS2 score ≥ 1 received a vitamin K antagonist (alone or in combination with an antiplatelet), 19.3% received aspirin alone, and 23.4% received no antithrombotic therapy; 3.6% of the patients received dual antiplatelet therapy and 1.1% clopidogrel alone. Over half of the patients (56.3%) were treated in accordance with the ESC 2010 guidelines. Of the remaining patients, 19.4% received no treatment, 13.0% were inadequately treated, and 11.2% were over-treated. Factors associated with antithrombotic treatment were anti-arrhythmic therapy, higher stroke risk, presence of atherothrombotic disease, and use of non-steroidal anti-inflammatory drugs. Female gender was associated with a lower likelihood of antithrombotic treatment.

Conclusions. — In this large French study, approximately 45% of thromboembolic high-risk patients were either not treated or inadequately treated. Better compliance with evidence-based guidelines is needed to reduce the burden of stroke in the AF population.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is frequently encountered in the primary care setting. The lifetime risk for developing AF or atrial flutter at 40 years of age is estimated to be 26% for men and 23% for women [1]. AF affects between 600,000 and 1 million patients in France [2,3]. Given the ageing population and the increasing prevalence of risk factors for AF, including hypertension, heart failure, older age, diabetes mellitus and vascular disease [4], the burden of AF in western populations is predicted to rise to epidemic proportions by 2050 [5].

Patients with AF are at increased risk of thrombotic events, including stroke and systemic embolism. Evidence-based guidelines recommend individualized risk stratification with validated tools and the use of oral anticoagulant (OAC) therapy for those identified to be at moderate or high risk of stroke [6,7]. For more than six decades, the only oral anticoagulants available for long-term use have been the vitamin K antagonists (VKAs; e.g. warfarin) [8]. While effective in preventing thromboembolism, VKAs have
In France, anticoagulant prophylaxis for patients with AF is managed largely in the primary care setting. General practitioners (GPs) play a pivotal role in the long-term management of these patients. Adherence to practice guidelines for stroke prevention and effective collaboration between GPs and cardiologists, or other specialists, are therefore essential. In this analysis, we investigated the antithrombotic prescription behaviours of GPs in France and compared them with the recommendations in the 2010 and 2012 European Society of Cardiology (ESC) guidelines for stroke prevention in AF [6,7]. We also identified the major determinants of use of antithrombotic therapy.

Methods

Using data from the French Longitudinal Patient Database (LPD; Cegedim Strategic Data, France), a medical records and prescriptions database [14], we conducted a cross-sectional survey on the use of antithrombotic treatments for stroke prevention in patients with AF. Since 1994, the LPD has collected anonymized data from more than 1.6 million patients through a computerized network of 1200 office-based GPs. The panel of physicians is representative of French GPs in terms of their age, sex, and geography. GPs do not receive direct compensation for participating in the database. The Commission Nationale de l'Informatique et des Libertés approved the use of the LPD data for analysis and patient informed consent was not required.

Study population and data extracted

The study population comprised adults (≥18 years of age) with a diagnosis of AF who attended at least one GP consultation between 1 July 2010 and 30 June 2011. During this period, data were collected on patient baseline characteristics, risk factors for stroke (i.e. congestive heart failure, left ventricular dysfunction, hypertension, diabetes mellitus, stroke, transient ischaemic attack, systemic embolism, vascular pathology), and prescription of VKAs and antiplatelet drugs.

Evaluation of stroke risk

Each patient’s risk of stroke was evaluated retrospectively using the CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischaemic attack [doubled]) criteria. A CHADS2 score of 0 was taken as indicative of low risk, 1 as moderate risk, and ≥2 as high risk. In addition, the patients’ CHA2DS2-VASc (cardiac failure or dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, age 65–74, and sex category [female]) scores were calculated, with the caveat that this score was included in the 2012 ESC guidelines [15], and was not therefore incorporated into normal practice at the time the data were collected. Treatment with antithrombotic drugs for stroke prevention in AF (VKAs and antiplatelets) was evaluated according to the 2010/2012 ESC guideline recommendations [6,7]. Inadequate treatment was defined as the use of aspirin instead of OAC in moderate- to high-risk patients and over treatment was defined as the use of OAC instead of aspirin in low-risk patients.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as frequency (percentage). The choice of treatment with VKA alone, aspirin alone, or VKA plus aspirin was studied in a binary manner (treatment vs. no treatment). Potential determinants of treatment (vs. no treatment) were identified from patient baseline and disease characteristics, medical history, and concomitant treatments. The analysis was performed using the GLIMMIX (SAS 9.2, SAS Institute Inc., Cary, NC, USA) procedure [16] for multivariable analysis, with the variable ‘physician’ taken as a random effect. Factors associated with treatment (vs. no treatment) that were significant at the 20% threshold in univariate analysis were included in a backwards elimination multivariable logistic regression model; factors significant at the 0.001 level were retained in the final model. All pairwise interactions were tested. CHADS2 or CHA2DS2-VASc scores were introduced into the final models to determine whether they were major determinants of antithrombotic therapy use. Results are presented with odds ratios (ORs) and their 95% confidence intervals (CIs).

Results

Study population

A total of 15,623 patients with AF were identified. The mean age was 74.6 ± 11.1 years, 59.5% were men, and 5.1% had valvular disease (Table 1). The overall mean body mass index (BMI) was 27.9 ± 5.3 kg/m²; 27.9% of the patients had a BMI between 20 and 25 kg/m² and 4.1% had a BMI below 20 kg/m². Of the patients in whom the type of AF was known, 77.4% had paroxysmal AF, 2.7% had persistent AF and 20.0% had permanent AF. The mean CHADS2 score was 1.5 ± 1.1 and 83.1% had a CHADS2 score ≥1. The mean CHA2DS2-VASc score was 2.9 ± 1.5 and 93.6% had a CHA2DS2-VASc score ≥1.

Antithrombotic treatment in patients at risk of stroke

Over half (52.6%) of the patients with a CHADS2 score ≥1 received a VKA (alone or in combination with an antiplatelet), 19.3% received aspirin alone, and 23.4%
Table 1  Patient characteristics, treatments, and risk level for stroke, overall and according to use of antithrombotic therapy at inclusion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>No antithrombotic therapy (n = 3924)</th>
<th>Antithrombotic therapy (n = 11,699)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 15,623)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>9291 (59.5)</td>
<td>2115 (53.9)</td>
<td>7176 (61.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.6 ± 11.1</td>
<td>74.2 ± 13.1</td>
<td>74.7 ± 10.4</td>
</tr>
<tr>
<td>Age ≥ 75 (years)</td>
<td>8981 (57.5)</td>
<td>2265 (57.7)</td>
<td>6716 (57.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.9 ± 5.3</td>
<td>26.9 ± 5.0</td>
<td>28.1 ± 5.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133 ± 15</td>
<td>133 ± 16</td>
<td>133 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 9</td>
<td>76 ± 10</td>
<td>76 ± 9</td>
</tr>
</tbody>
</table>

Medical history

- Arterial hypertension: 9246 (59.2) vs. 1934 (49.3) vs. 7312 (62.5)
- Diabetes mellitus: 2683 (17.2) vs. 513 (13.1) vs. 2170 (18.5)
- Heart failure: 1775 (11.4) vs. 347 (8.8) vs. 1428 (12.2)
- Stroke: 763 (4.9) vs. 157 (4.0) vs. 606 (5.2)
- TIA: 502 (3.2) vs. 82 (2.1) vs. 420 (3.6)
- Systemic embolism: 97 (0.6) vs. 8 (0.2) vs. 89 (0.8)
- Myocardial infarction: 665 (4.3) vs. 108 (2.8) vs. 557 (4.8)
- Prosthetic heart valve: 309 (2.0) vs. 54 (1.4) vs. 255 (2.2)
- Neurological disorders: 422 (2.7) vs. 134 (3.4) vs. 288 (2.5)
- PAD: 827 (5.3) vs. 138 (3.5) vs. 689 (5.9)
- Valvular disease: 795 (5.1) vs. 186 (4.7) vs. 609 (5.2)

Type of AF<sup>d</sup>

- Paroxysmal: 1891 (77.4) vs. 513 (84.0) vs. 1378 (75.2)
- Permanent: 488 (20.0) vs. 88 (14.4) vs. 400 (21.8)
- Persistent: 65 (2.7) vs. 10 (1.6) vs. 55 (3.0)

Concomitant drugs

- Non-steroidal anti-inflammatory drug: 7492 (48.0) vs. 1305 (33.3) vs. 6187 (52.9)
- Anti-arrhythmic drug: 7425 (47.5) vs. 834 (21.3) vs. 6591 (56.3)
- Injectable anticoagulants (e.g. heparin): 482 (3.1) vs. 83 (2.1) vs. 399 (3.4)

Risk scores for stroke

- CHADS<sub>2</sub> score (%): 2638 (16.9) vs. 887 (22.6) vs. 1751 (15.0)
- 1: 5026 (32.2) vs. 1342 (34.2) vs. 3684 (31.5)
- ≥ 2: 7959 (50.9) vs. 1695 (43.2) vs. 6264 (53.5)

- CHA<sub>2</sub>D<sub>2</sub>-VASc score (%): 998 (6.4) vs. 399 (10.2) vs. 599 (5.1)
- 1: 1774 (11.4) vs. 499 (12.7) vs. 1275 (10.9)
- ≥ 2: 12,851 (82.3) vs. 3026 (77.1) vs. 9825 (84.0)

Percentages were calculated on the basis of the total number of known data. Values are given as number (%) or mean ± SD.

<sup>a</sup> Available for 8390 patients.
<sup>b</sup> Available for 12,932 patients.
<sup>c</sup> Available for 12,926 patients.
<sup>d</sup> Available for 2444 patients.

received no antithrombotic therapy (Fig. 1). A small percentage of patients received dual antiplatelet therapy (3.6%) and 1.1% received clopidogrel alone.

Over half of the patients (56.3%) were treated in accordance with the recommendations in the ESC 2010 guidelines [6] (Fig. 2A). Of the remaining patients, 19.4% of patients received no treatment, 13.0% were inadequately treated, and 11.2% of patients were over-treated. In patients with a CHADS<sub>2</sub> score of 0, who are at low risk of a stroke and do not require OAC prophylaxis, 66.4% were over-treated (Fig. 2A). Patients with a CHADS<sub>2</sub> score of 1 were the most likely of any of the risk groups to receive guideline-recommended therapy (70.4%). Over half (54.9%, n = 4372) of those at highest risk (CHADS<sub>2</sub> score ≥ 2) and 52.4% (n = 6740) with a CHA<sub>2</sub>D<sub>2</sub>-VASc ≥ 2 received anticoagulant therapy (Fig. 2A, 2B).

In terms of the ESC 2012 guidelines [7], which advocate the CHA<sub>2</sub>D<sub>2</sub>-VASc score for risk stratification, the proportion of patients who received guideline-recommended therapies decreased for patients with a score of 1 or ≥ 2 compared with the ESC 2010 recommendations (Fig. 2B). This difference was due largely to a higher rate of inadequate treatment in patients at moderate risk, and to higher rates of inadequate treatment or no treatment in those at high risk.
Factors associated with antithrombotic treatment

The strongest factor associated with antithrombotic treatment was the use of anti-arrhythmic therapy (Tables 2 and 3). Higher stroke risk, presence of atherothrombotic disease, and use of non-steroidal anti-inflammatory drugs were also associated with greater likelihood of antithrombotic therapy use whereas female gender was associated with a lower likelihood.

Discussion

These nationwide French data indicate that over four-fifths of AF patients treated in the primary care setting are at moderate to high risk of a stroke and should be considered for anticoagulant treatment. A large percentage of the patients at high risk are inadequately treated, leaving them unprotected against a thromboembolic event, and many of those at low risk are over-treated, placing them at unnecessary risk of a treatment-associated bleeding event. These findings indicate a treatment gap between the recommendations in practice guidelines [6,7] and everyday clinical practice.

Comparison with other studies

Our findings are in concert with some studies, which indicate disappointing rates of OAC use for stroke prevention in the AF population [12,13,17]. They are also much lower than the rates reported in other studies, such as the French European Public Health Alliance (EPHA) study (83.4% on VKAs) [18], the Prevention of thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF) registry (> 80% on OACs) [19], the EURObservational Research Programme—Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot) registry (approximately 78% on OACs) [20], the German Outpatient Registry Upon Morbidity of Atrial Fibrillation (ATRIUM) (82.7% on OAC) [21], the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) (83.0% of patients without contraindications to OAC) [22], and a cross-sectional study conducted in the Netherlands (69% on OAC) [23]. Several key reasons can be proposed for these variations in practice patterns. The first concerns the profile of the study population, as the characteristics and risk profiles of patients in hospital registries differ from those of outpatients in general practice. The second concerns provider specialty and treatment setting, with higher levels of OAC use provided by specialists versus primary care/ internal medicine providers [24] and better adherence to evidence-based guidelines in hospitals versus non-hospital settings [25]. The third concerns the methodology adopted. Prospectively enrolled patients in observational studies are subject to selection bias. In contrast, the present study was based on a primary care database and presents a "pure" view of everyday practice patterns, as neither the physician nor the patient was aware of the study at the time of the consultation. Furthermore, the management of anticoagulants in France, including dosing in relation to international normalized ratio for patients on VKAs, is conducted by GPs, whereas in other European countries such patients may attend specialized anticoagulation clinics.

Barriers to anticoagulation

Often patients are not treated according to guidelines because of the physician’s perception of their individual
risk of stroke (or haemorrhage), which may be at variance to the level indicated by validated risk scores [12,26–28]. Women are at increased risk of stroke when compared with men [29], yet female sex was associated with lower rates of OAC use in our study. Current data also suggest that OAC use varies according to the type of treating physician, with higher rates of use in patients treated by a cardiologist or electrophysiologist versus a primary care physician [24]. Use of OAC was high among AF patients treated by cardiologists in the EPHA study [18] and the EORP-AF Pilot registry [20]. In contrast, much lower rates are reported in studies, such as the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) [12], which reflects management across the spectrum of care settings treating the AF community, including office-based specialists, hospital departments, anticoagulant clinics, and general or family practice settings. Furthermore, the recommendation to use risk stratification schemes, such as CHADS2 and CHA2DS2-VASc to determine risk level is relatively recent and it appears likely that hospital-based physicians are more accepting of the value of practice guidelines than are physicians involved in outpatient care [25]. While the recommendations for prevention of thromboembolism in patients with a score ≥ 2 (whether by CHADS2 or CHA2DS2-VASc) are clear, the situation in patients with a score of 1 is more complex, with physicians facing further choices regarding the optimal treatment strategy (Table 4).

### Table 2 Factors associated with antithrombotic treatment in atrial fibrillation, with CHADS2 score forced into the model (based on data from all 15,623 patients).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmic (ref: no anti-arrhythmic)</td>
<td>4.70 (4.30–5.14)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CHADS2 score (ref: score of 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>2.13 (1.91–2.38)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>1</td>
<td>1.52 (1.36–1.70)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NSAID (ref: no NSAID)</td>
<td>2.09 (1.92–2.27)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Atherothrombotic diseasea (ref: no atherothrombotic disease)</td>
<td>1.48 (1.30–1.70)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female sex (ref: male)</td>
<td>0.65 (0.60–0.70)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio.

### Anticoagulant treatments for stroke prevention

OACs for stroke prevention have been limited to VKAs, such as warfarin, for over six decades [8]. A meta-analysis of 29 clinical trials in 28,044 participants demonstrated that adjusted-dose warfarin reduced the risk of stroke by 64% (95% CI 49–74) was more effective than antiplatelet therapy for stroke prevention (relative risk reduction 39%, 95% CI 22–52), and absolute increases in major extracranial haemorrhage were small (< 0.3% per year) [30]. However, the rate of major haemorrhage in practice may be much higher, as suggested by data from a population-based cohort survey of more than 125,000 warfarin-treated patients (3.8%, 95% CI 3.8–3.9), particularly during the first month of treatment (11.8%, 95% CI 11.1–12.5) [31]. One of the major limitations of VKA therapy is difficulty maintaining the target international normalized ratio (2–3) [19,32]. Recently published data from the LPD indicated that < 50% of patients with AF in France, Germany and Italy had well-controlled VKA treatment (defined as a time in therapeutic range > 70%) [33]. This may be partly due to the substantial difficulties patients experience adhering to the warfarin regimen, with one study reporting that 36% of patients miss > 20% of their doses [34]. Suboptimal anticoagulation with VKAs is associated with an increased risk of stroke, particularly during the first 30 days [32,35]. Concern over treatment-related bleeding complications, especially in the elderly [36], is in part

### Table 3 Factors associated with antithrombotic treatment in atrial fibrillation, with CHA2DS2-VASc score forced into the model (based on data from all 15,623 patients).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmic (ref: no anti-arrhythmic)</td>
<td>4.72 (4.31–5.16)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (ref: score of 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>3.11 (2.66–3.64)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>1</td>
<td>2.09 (1.74–2.51)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NSAID (ref: no NSAID)</td>
<td>2.10 (1.93–2.28)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Atherothrombotic diseasea (ref: no atherothrombotic disease)</td>
<td>1.50 (1.30–1.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female sex (ref: male)</td>
<td>0.58 (0.53–0.63)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio.

a Peripheral artery disease, systemic embolism, myocardial infarction, stroke or transient ischaemic attack.
Table 4  ESC recommendations for antithrombotic therapy in patients with AF.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-valvular AF CHADS2 0</td>
<td>No antithrombotic therapy (or aspirin) (Class I, level of evidence B)</td>
<td>Strong recommendation to use the CHA2DS2-VASc risk score to focus on identification of &quot;truly low-risk&quot; patients with non-valvular AF</td>
</tr>
<tr>
<td>CHADS2 1</td>
<td>OAC (Class I, level of evidence A) or aspirin (Class I, level of evidence B)</td>
<td>No antithrombotic therapy (Class I, level of evidence B)</td>
</tr>
<tr>
<td>CHADS2 ≥ 2</td>
<td>OAC (Class I, level of evidence A)</td>
<td>OAC should be considered according to individual risk and patient preference (Class IIa, level of evidence A)</td>
</tr>
<tr>
<td>CHA2DS2-VASc 0</td>
<td>No antithrombotic therapy (preferred) or aspirin</td>
<td>No antithrombotic therapy in women &lt; 65 years with lone AF (i.e. no other risk factors for thromboembolism) (Class IIa, level of evidence B)</td>
</tr>
<tr>
<td>CHA2DS2-VASc 1</td>
<td>OAC (preferred) or aspirin</td>
<td>OAC (Class I, level of evidence A) in patients without contraindications</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≥ 2</td>
<td>OAC</td>
<td>Valvular AF (i.e. AF related to rheumatic valvular disease [predominantly mitral stenosis] or prosthetic heart valves)</td>
</tr>
<tr>
<td>AF and valvular heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>Valvular heart disease</td>
<td>Assess each patient’s risk of stroke using the CHA2DS2-VASc score and treat as for non-valvular AF</td>
</tr>
<tr>
<td>Risk assessment and antithrombotic therapy</td>
<td>OAC in patients with mitral stenosis and AF (Class I, level of evidence C) OAC in patients with clinically significant mitral regurgitation (Class I, level of evidence C)</td>
<td></td>
</tr>
</tbody>
</table>

Responsible for the failure to provide adequate prophylaxis. An analysis from the UK General Practice Research Database demonstrated that 30% of patients starting warfarin therapy discontinue the medication within 12 months [37]. Consequently, substantial efforts have been made over the past decade to identify OACs that overcome some of the limitations of VKAs and that have at least equivalent efficacy, with a reduced risk of bleeding, and are more convenient to use for both patients and physicians [38]. This research has led to the introduction of the non-VKA oral anticoagulants (NOACs), comprising the oral direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban. Edoxaban has been approved recently by the US Food and Drug Administration (FDA), but is not currently available on the market. These treatments have at least similar efficacy to VKAs, with predictable pharmacokinetics, a stable dose-related treatment effect, and few drug interactions, enabling fixed dosing without the need for regular laboratory monitoring [39,40].

In response to the clinical trial evidence demonstrating their net clinical benefit, the 2012 ESC guidelines recommend NOACs over adjusted-dose VKAs (Class IIa, level of evidence A) for most patients aged 65 years or older with non-valvular AF [7]. In France, economic evaluations have demonstrated that NOACs are an efficient alternative to warfarin in patients with non-valvular AF who are eligible for stroke prevention [41,42]. NOACs also present a suggested option in patients with poorly controlled VKAs, for pharmacological reasons and based on epidemiological data, after a cautious evaluation of patient compliance by the GP or cardiologist. The ESC Working Group on Thrombosis recommends using a decision-making tool (sex female, age < 60 years, medial history [more than two comorbidities], treatment [interacting drugs, e.g. amiodarone for rhythm control], tobacco use [doubled], race [doubled]; SAme-TT2R2) to identify patients likely to do well on VKAs (score of 0–2) and those more likely to have poor anticoagulation control (score > 2) who would probably benefit from starting a NOAC as the initial therapy [8].

Strategies to improve adherence to guidelines

The European guidelines on AF [6] were published midway through 2010, with an update in 2012 [7] (Table 4). Our data reflect practices taking place during 2010 and 2011 and do not take into account the inevitable "lag" that occurs between publication of guidelines and implementation in practice. Assuming that sufficient time has elapsed since the publication of these guidelines, we would anticipate and hope that current practice more closely mirrors the recommendations in these guidelines. To act on such recommendations, however, physicians need to be aware of
the real risk of stroke in their AF patients and be convinced that the guidelines are based on compelling evidence from well-designed controlled clinical trials. Furthermore, recent data indicate that NOACs are indeed being incorporated into clinical practice, but there is as yet no indication that the overall rates of OAC use are improving [43,44]. There remains, therefore, an urgent need to address the barriers to optimal OAC use and persistence in the AF population. In France, stroke physicians launched a national action plan entitled "Stroke 2010–2014", the aim of which was to develop stroke care networks and strategies for prevention and health education [45]. The plan is now shared with other health professionals, and more recently with administrators and politicians.

A think-tank, comprising leaders from academia, government, industry and professional societies, was convened in the United States in 2012 to identify strategies to improve stroke prevention. Their recommendations are wide ranging, and encompass the identification of reasons for OAC underuse, educational initiatives that will raise awareness of stroke risk and the benefits of OAC treatment, the provision of decision-making tools and feedback performance in terms of OAC use, and defining the population who would benefit from VKA (rather than NOAC) treatment [46]. Additional efforts are needed to improve the time in therapeutic range for patients on VKAs.

While the half-life of the NOACs is relatively short and their anticoagulant effect has largely disappeared after 1−2 days, investigations are being conducted to identify specific antidotes to reverse their effects [46]. Andexanet alfa, designated a breakthrough therapy by the US FDA, is being investigated as an antidote to factor Xa inhibitors in two phase 3 studies (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors [ANNEXA]). The results for ANNEXA-A were presented at the 2014 American Heart Association Congress, and showed that andexanet alfa administration was well tolerated in older subjects (age 55 to 73 years), and met all of the pre-specified primary and secondary efficacy endpoints (all \( P < 0.0001 \)). All of the andexanet-treated patients had \( >90\% \) reversal of anti-fXa activity and restoration of thrombin generation to baseline (pre-anticoagulant) levels. There was a near-complete normalization of all coagulation variables measured within 2 minutes of completion of infusion. A phase 3 study will aim to demonstrate that prolonged reversal can be sustained with continuous infusion after bolus administration [46].

Study limitations

The LPD database provides representative data from patients treated in practice and as such is not subject to ascertainment bias. However, several limitations must be noted. The data are prone to information bias as no restrictions were imposed on GPs in terms of the data collection. The information collected is restricted to GP practices, and excludes any management outside of primary care by, for example, cardiologist or other specialists. However, in view of the 12-month follow-up, which included prescription renewal data, patients are unlikely to have been incorrectly classified in terms of the various treatment groups. Information on contraindications to OAC therapy or patient refusal to take therapy was not available, so the proportions of patients who were under-treated or who received no treatment are likely to be slightly elevated. Data were collected during GP consultations and it is unlikely that they were able to collect all determinants for prescription choice. Variables that may influence anticoagulant prescription may have been unavailable. Finally, the survey was completed in 2011, before publication of the updated ESC guidelines for AF [7], and the results may not be reflective of current practices.

Conclusions

In this large study based on data from the French primary care setting, four out of five patients diagnosed with AF should benefit from stroke prophylaxis. Around 45% of thromboembolic high-risk patients either are not treated or are inadequately treated. Better compliance with evidence-based guidelines and improved collaboration between GPs and cardiologists is needed in order to reduce the burden of stroke in the AF population.

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Disclosure of interest

PS has undertaken consultancy for the present study. MB, MAH, FEC, LDB are employees of Bristol-Myers Squibb, manufacturer of apixaban. SRS has undertaken consultancy for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, European Society of Cardiology, MSD and Sanofi.

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